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| 09/492,590 | 01/27/2000 | Carsten-Peter Cartens | 41114/85530 | 1053 |

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| EXAMINER |
|---|
| LEFFERS JR, GERALD G |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/492,590 | CARTENS, CARSTEN-PETER | |
| | Examiner | Art Unit | |
| | Gerald G Leffers Jr. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16 and 18-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 18-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *25* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Continued Prosecution Application*

The request filed on 9/26/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/492,590 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 1-16, 18-44 are pending in this application.

Any rejection of record in the previous office actions that has not been addressed in this action is withdrawn. Because new grounds of rejection are raised herein, this action is not final.

### *Interview Summary*

Enclosed is a copy of an interview summary for an interview conducted on 9/20/02 between the examiner and Mr. Mark Fitzgerald.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-5, 10-16, 22-23, 26-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al (U) in view of Nakamura et al, Zhang et al, Saier, Sprinzl et al, Kawakami et al and Clouthier et al (see applicants' exhibits A-G). **This is a new rejection.**

Del Tito et al teach the construction and use of a plasmid, pRI952, which comprises an array of two tRNA genes (argU and IleX) encoding tRNAs specific for the rarely used codons AGG/AGA and AUA, respectively (e.g. page 7087, paragraph 2; Tables I and II). The authors teach that PRI952 was constructed by insertion of a PCR-amplified DNA comprising the gene for ileX flanked by HindIII restriction sites into pDC592, a pACYC184 derivative (i.e. low copy number plasmid) already possessing the argU gene (e.g. pages 7087, column 2, paragraph 2). Del Tito et al teach that coexpression of the two tRNA genes along with the gene encoding the heterologous polypeptide Mup$^r$ IRS results in increased levels of active protein as compared to a control in which no additional tRNA genes are expressed or as compared to cells comprising a plasmid only expressing the ileX gene (e.g Table II). Del Tito et al teach that "...problems in expression can be avoided by a careful inspection of the coding sequence and inclusion of appropriate tRNA genes or necessary site-specific mutations." (page 7087, column 1, paragraph 2). The authors conclude that the co-expression of minor tRNAs such as ileX or argU can be utilized to overcome translational stresses due to the presence of rarely used codons within the coding sequence for a gene of interest (e.g. page 7091, column 1, paragraph 3). Del Tito et al teach the purification by reverse-phase HPLC of another heterologous polypeptide (i.e. the B/LeeHA antigen) produced by their system for compensating for the presence of rare codons in the coding sequence for the desired polypeptide (e.g. page 7088, column 1, paragraphs 3-4).

Del Tito et al do not explicitly teach the use of a vector comprising an array of two or three or more tRNAs corresponding to rarely used codons for overexpression of a heterologous gene comprising rarely used codons for any species other than E. coli.

Nakamura et al (Nucleic Acids Research, 1996, Vol. 24, pages 214-215; see the entire reference) provide codon usage data tabulated from the GenBank international DNA sequence databases for 4,805 species (e.g. prokaryotes, protozoa, fungi, animals and plants).

Zhang et al (Gene, 1991, pages 61-72, see the entire reference) detail low usage codons in species as diverse as E. coli, yeast, Drosophila and primates.

Saier, M. H. (FEBS, 1995, Vol. 362, pages 1-4; see the entire document) teaches the rare codon usage in several different species (e.g. R. capsulatus, R. speriodes, C. acetobutylicum, S. coelicular and E. coli).

Sprinzl et al (Nucleic Acids Research, 1984, Vol. 12, supplement, pages r89-r130); see the entire document) teach a compilation of 353 sequences of tRNA genes including cellular and mitochondrial tRNAs from bacteria and phage, plants, yeasts and fungi, insects, amphibians and mammals, including rats, mice, cows and humans.

Kawakami et al (1993, Genetics, Vol. 135, pages 309-320; see the entire document) teach a rare Arg-tRNA-CCU in S. cerevisiae).

Clouthier et al (J. Bacteriology, 1998, Vol. 180, pages 840-845, see the entire document) teach a rare Arg-tRNA-AGA from S. enteritidis.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the vector construct taught by Del Tito et al for compensating for the presence of rarely used codons present in the gene encoding a protein of interest by interchanging and/or

adding different tRNA genes corresponding to other rarely used codons in a given cell type, because Del Tito et al teach that it is within the skill of the art to carefully scrutinize the coding sequence of a protein, identify rarely used codons and compensate for the presence of such rarely codons by supplying in trans the tRNA corresponding to the identified rarely used codons from a vector expressing different tRNA genes, and because the rarely used codons and corresponding genes were widely known in the art (i.e. the teachings of Nakamura et al, Zhang et al, Saier, Sprinzl et al, Kawakami et al and Clouthier et al). One would have been motivated to do so in order to meet the particular rare-codon requirements of a gene encoding a desired protein in combination with a given cell type, and thus receive the expected benefit of increasing its expression in the given cell type, as taught by Del Tito et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing any tRNA gene obtained from any cell type that was known in the art (i.e. ileY, proL, leuW, etc.) in the approach taught by Del Tito et al to increase the production of a desired protein that comprises rarely used codons.

Claims 1-5, 10-16, 22-23 and 26-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al (U) in view of Makoff et al (V). **This rejection is maintained for reasons of record in Paper No. 12, mailed 5/9/01. Applicant's arguments filed in Paper No. 24, mailed 9/26/02, have been fully considered but they are not persuasive for reasons given in the Response to Arguments below.**

Claims 6-9, 19, 21 and 24-25 are rejected under 35 U.S.C. 103(a) as being obvious over Del Tito et al (U) in view of Makoff et al (V) as applied to claims 1-5, 10-17, 22-23 and 26-38 above, and further in view of the 1997 Novagen catalog (pages 42-44) (W). **This rejection is maintained for reasons of record in Paper No. 12, mailed 5/9/01. Applicant's arguments filed in Paper No. 24, mailed 9/26/02, have been fully considered but they are not persuasive for reasons given in the Response to Arguments below.**

Claims 18 and 20 are rejected under 35 U.S.C. 103(a) as being obvious over Claims 6-9, 19, 21 and 24-25 are rejected under 35 U.S.C. 103(a) as being obvious over Del Tito et al (U) in view of Makoff et al (V) and the 1997 Novagen catalog (pages 42-44) (W) as applied to claims 1-17, 19 and 21-38 above, and further in view of Wnendt (X). **This rejection is maintained for reasons of record in Paper No. 12, mailed 5/9/01. Applicant's arguments filed in Paper No. 24, mailed 9/26/02, have been fully considered but they are not persuasive for reasons given in the Response to Arguments below.**

Claims 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al (U). **This rejection is maintained for reasons of record in Paper No. 12, mailed 5/9/01. Applicant's arguments filed in Paper No. 24, mailed 9/26/02, have been fully considered but they are not persuasive for reasons given in the Response to Arguments below.**

***Response to Arguments/35 USC 103(a) Rejections***

Applicant's arguments filed in Paper No. 24 have been fully considered but they are not persuasive. The response filed in Paper 24 reiterates many of the same arguments made in previous responses (Papers No. 11 and 17). Examiner's comments in Papers No. 12 and 19 are incorporated herein in response. The response filed in Paper No. 24 essentially argues: 1) the law does not absolutely require evidence of market share in order for commercial sales of a product of an invention to be persuasive of nonobviousness, and that the commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art (e.g. *Richdel, Inc., v. Sunspool Corp*), 2) the law has indicated that a primary showing of commercial success limited to sales, coupled with a demonstration that the commercial success of the product derives from the claimed invention and is attributable to something disclosed in the patent that was not readily available in the prior art is entitled to the presumption that the commercial success of the product is attributable to the patented invention (*J.T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.*), 3) the Buchanan Declarations support the conclusion that the products sold are embodiments of the claimed invention, and 4) under J.T. Eaton, applicants are entitled to the presumption that the commercial success of the product is attributable to the claimed invention. The response of Paper No. 24 further argues that because the product sold upon which the arguments of commercial success is based is usable in the host cell upon which the 103(a) rejections are based, any finding that the commercial success arguments for embodiments sold by the Assignee are valid (i.e. E. coli embodiments are non-obvious), then there is no reason to conclude that embodiments encompassing other cell types, for which there is a lack of relevant prior art, would also be non-obvious.

As indicated above, and in the previous arguments presented in Papers No. 12 and 19, the evidence of record does not indicate that the level of commercial sales of a couple of specific embodiments of the claimed invention is necessarily due to some aspect of the claimed invention. Without the appropriate background against which to judge (e.g. a commercially available vector comprising the tRNA genes taught by Del Tito et al), it is impossible to make the judgment that there is some aspect of applicants' invention that contributes to significant commercial success or that the demonstrated sales are of such a magnitude as to make the claimed invention unobvious over the prior art.

Also, with regard to the cited arguments framed in context of *Richdel, Inc., v. Sunspool Corp* and *J.T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.*, it is not conceded based upon the evidence presented to date in prosecution that applicants have established that the purported commercial success of a few specific embodiments of their invention is 1) due to the merits of the claimed invention beyond what was readily available in the prior art, or 2) derives from the claimed invention and that is attributable to something disclosed in the patent that was not readily available in the prior art. In other words, all of the elements of the claimed invention were readily available in the art at the time of the claimed invention.

As was demonstrated in making the rejection, the basic concept of supplying different rarely used tRNA genes in a cell to maximize expression of a desired gene product was clearly known at the time of filing and the raw materials (i.e. rare tRNA genes and rarely-used codons) were readily available in the art at the time of filing. The authors of the base reference, Del Tito et al, teach that "...problems in expression can be avoided by a careful inspection of the coding sequence and inclusion of appropriate tRNA genes or necessary site-specific mutations." (page

7087, column 1, paragraph 2). Del Tito et al conclude that the coexpression of minor tRNAs such as ileX or argU can be utilized to overcome translational stresses due to the presence of rarely used codons within the coding sequence for a gene of interest (page 7091, column 1, paragraph 3). The claimed invention differs from the teachings of Del Tito et al *only* in the exact tRNA genes, and/or, in the number of tRNA genes that are comprised within the DNA constructs of the invention. The originally filed claims drawn to embodiments comprising two tRNA genes comprised a specific negative limitation that the set of two tRNA genes did not consist of the two tRNA genes taught by Del Tito et al. Emdodiments drawn towards an array of three or more tRNA genes only differ from the embodiment taught by Del Tito et al by the addition of another tRNA gene.

That it was known in the art how to express more than just two genes from a single construct is readily demonstrated by any teaching of the prior art where at least three coding sequences are expressed from the same construct (e.g. in Del Tito et al where ileX, argU, and an antibiotic-resistance marker are expressed). The assertion by the examiner in making the rejection that the tRNA genes and rare codon usages for numerous organisms were known in the art at the time of invention is supported by the documents attached to applicants' response in Paper No. 24 (Exhibits A-G) to overcome a 112 1st rejection for lack of written description. Given that the basic concept that is the crucial element of the invention was already known in the art (i.e. providing tRNAs corresponding to rarely used codons from DNA constructs comprising the cognate tRNA genes), that applicants' invention differs only in the make-up of the DNA constructs that are used to express the tRNA genes, and that the means and materials for making the changes necessary to the constructs taught by Del Tito et al in order to arrive at the claimed

invention, it is the examiner's conclusion that there is no significant contribution from the instant application that was not already readily available from the prior art. Therefore, the arguments based upon *Richdel, Inc., v. Sunspool Corp* and *J.T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.* do not apply against this rejection.

Finally, the argument that, because both the cited prior art teachings and the specific embodiments upon which commercial success is asserted function in E. coli, embodiments that function outside of E. coli are also unobvious, is not persuasive. This argument is based upon the assertion that there is a lack of relevant prior art for embodiments featuring cell types other than E. coli. Applicants' submission of Exhibits A-G in Paper No. 24 amply demonstrates that the tRNA genes and codon usages for a very large number of different organisms was known in the art at the time of the invention. Thus, it would have been prima facie obvious in view of the teachings of Del Tito et al to construct vectors comprising tRNA genes corresponding to rarely used codons from species other than E. coli (see above). Finally, there is no evidence of record that whatever commercial success seen for embodiments that function in E. coli would necessarily be observed for embodiments that are intended for use in other cell types (e.g. maize, B. subtilis, S. aureus, D. melanogaster, etc.).

***Conclusion***

**No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

ggl
December 16, 2002